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Advanced HIV Disease in individuals already in care: incidence and comparison with late presentation

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BACKGROUND

Advanced HIV disease (AHD) remains a pressing health issue among people with HIV (PWH)[1,2]. Although traditionally perceived as related to late presentation to care, recent data from resource-limited settings indicated an increasing prevalence of AHD among PWH already in care, raising an emerging challenge in the HIV continuum of care[3,4] However, **limited data exist comparing characteristics and outcomes of late presenting PWH with those developing AHD despite prior engagement in care** [5,6].

METHODS

- POPULATION: **All PWH**, enrolled in the **Icona Foundation Study Cohort**, who received **a first diagnosis of AHD** [*CD4 count <200 cell/mm³ or AIDS-defining event (ADE), regardless of CD4 count]* between **Jan 2004 and Dec 2024** were included. Participants were categorized into: **1) Prevalent AHD (pAHD)** [*AHD diagnosed at the time of HIV diagnosis]* and **2) Incident AHD (iAHD)** [*AHD diagnosed >3 months after ART starting*]. Groups were further **stratified by the presence of ADE**.
- STUDY OBJECTIVES: **Primary objective**: to assess all-cause mortality risk in pAHD vs. iAHD; **Secondary objectives**: to evaluate temporal trends of AHD and compare key demographic/clinical characteristics in pAHD vs. iAHD.
- STATISTICS: Temporal trends: *pAHD risk, iAHD incident rate, risk of incident cases (iAHD/total AHD) by year*; Group comparisons ar AHD diagnosis: *Chi-square test for categorical and Mann–Whitney/Kruskal–Wallis test for continuous variables*; Mortality risk: *Kaplan-Meier curves and multivariate Cox regression, comparing pAHD vs iAHD, overall and after stratifying by ADE.*

Table 1: Participants 'characteristics at AHD diagnosis by exposure group

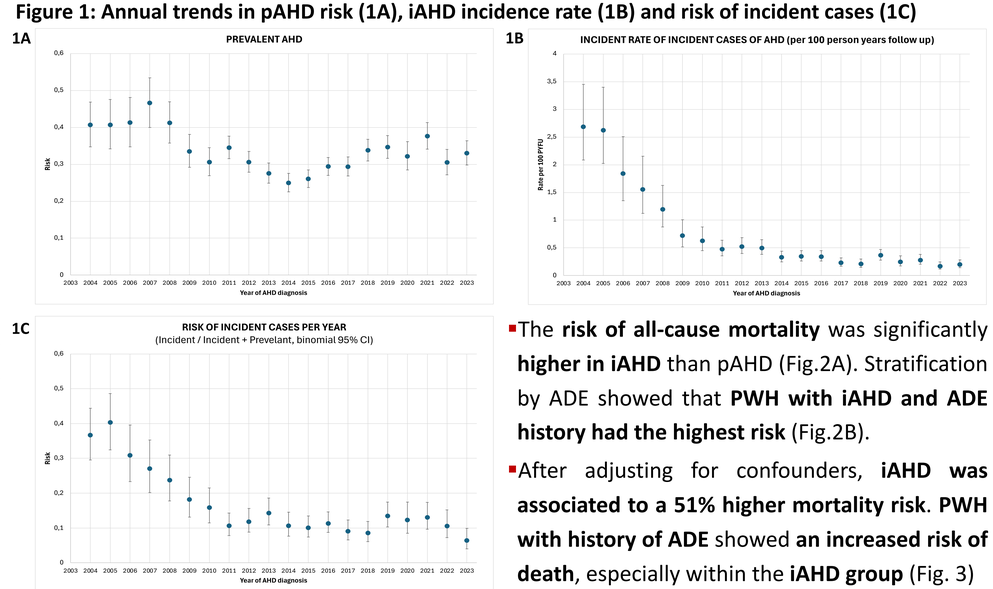
	PREVALENT AHD [n=4,799, 86%]	INCIDENT AHD [n=788, 14%]	TOTAL [n=5,587]	p-value
FEMALE GENDER, n (%)	1,092 (22.8%)	228 (28.9%)	1,320 (23.6%)	**0.001**
AGE, YEARS, median (IQR)	43 (35-52)	44 (37-51)	43 (36-52)	**0.002**
MODE OF HIV TRANSMISSION, n (%)				**<0.001**
Homosexual	1,524 (31.8%)	255 (32.4%)	1,779 (31.8%)	
Heterosexual	2,455 (51.2%)	316 (40.1%)	2,771 (49.6%)	
People who inject drugs	371 (7.7%)	177 (22.5%)	548 (9.8%)	
NOT ITALIAN NATIONALITY, n (%)	1,350 (28.1%)	126 (16.0%)	1,476 (26.4%)	**<0.001**
CD4 COUNT AT AHD, cells/mm³, median (IQR)	124 (71-165)	159 (109-185)	131 (77-170)	**<0.001**
HIV-RNA AT AHD, log_{10} copies/mL, median (IQR)	5.31 (4.78-5.79)	2.08 (1.40-4.67)	5.17 (4.44 -5.70)	**<0.001**
AIDS-defining event, n (%)	1,628 (33.9%)	269 (34.1%)	1897 (34.0%)	0.907
FIRST–LINE ART, n (%)				
- PI-based	1,686 (35.1%)	263 (33.4%)	1,949 (34.9%)	**0.022**
- NNRTI-based	562 (11.7%)	223 (28.3%)	785 (14.1%)	**<0.001**
- INSTI-based	1,941 (40.4%)	113 (14.3%)	2,054 (36.8%)	**<0.001**
COMORBIDITIES				
- Cardiovascular	55 (1.1%)	15 (1.9%)	70 (1.3%)	0.076
- Diabetes	124 (2.6%)	49 (6.2%)	173 (3.1%)	**<0.001**
- Hypertension	201 (4.2%)	84 (10.7%)	285 (5.1%)	**<0.001**
- Hepatitis co-infection	288 (6.1%)	228 (28.9%)	516 (9.2%)	**<0.001**
ALCHOL ABUSE (%)	79 (1.5%)	62 (7.9%)	141 (2.4%)	**<0.001**
SMOKING, n (%)	937 (19.5%)	328 (41.6%)	1,265 (22.6%)	**<0.001**
EDUCATION LEVEL, n (%)				**<0.001**
- Primary School	317 (6.6%)	64 (8.1%)	381 (6.8%)	
- Secondary School	2,139 (44.6%)	459 (58.2%)	2,598 (46.5 %)	
- College/University	421 (8.7%)	53 (6.7%)	474 (8.4%)	
EMPLOYMENT STATUS, n (%)				**<0.001**
- Unemployed	660 (13.7%)	121 (15.3%)	781 (14.0%)	
- Employed/self-employed	2,493 (51.9%)	470 (59.6%)	2,963 (53.0%)	
- Student/occasional	205 (4.3%)	40 (5.1%)	245(4.4%)	
- Retired/Housewife	339 (7.0%)	56 (7.1%)	408 (7.1%)	

Among PWH already in care in Italy, **the incidence of AHD has significantly declined over time.** Compared with newly diagnosed PWH, **those with AHD despite prior engagement in care had distinct demographic and clinical characteristics** and **experienced worse clinical outcomes**, with a significantly higher risk of all-cause mortality, **particularly in the presence of an ADE.**

RESULTS

- **5,587 PWH** included: **4,799 newly diagnosed (pAHD)** and **788 already in care (iAHD)** [**AHD** diagnosis was **due to ADE** in **33.9%** and **34.1%**, respectively]**.**
- **pAHD and iAHD differed for most demographic and clinical characteristics at AHD diagnosis** (Table 1). Notably, 1.7% pAHD and 5.6% iAHD did not start ART after AHD diagnosis while 15.8% pAHD and 7,5% iAHD started more than 30 days later.
- The **incidence of iAHD significantly declined** from 2.7 cases per 100 PYFU in 2004 (95%CI: 2.1–3.4) to <0.5 cases PYFU over the past decade, **accounting for <10% of all AHD cases in 2023** (Fig 1B,1C). In contrast, **the risk of pAHD exhibited a more variable trend** (Fig. 1A).

Figure 1: Annual trends in pAHD risk (1A), iAHD incidence rate (1B) and risk of incident cases (1C)



- The **risk of all-cause mortality** was significantly **higher in iAHD** than pAHD (Fig.2A). Stratification by ADE showed that **PWH with iAHD and ADE history had the highest risk** (Fig.2B).
- After adjusting for confounders, **iAHD was associated to a 51% higher mortality risk**. **PWH with history of ADE** showed **an increased risk of death**, especially within the **iAHD group** (Fig. 3)

Figure 2: Probability of all-cause mortality by exposure group (2A) and after stratification by ADE (2B)

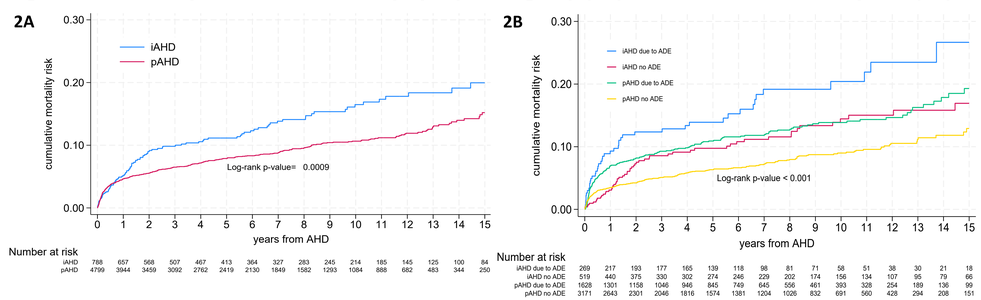
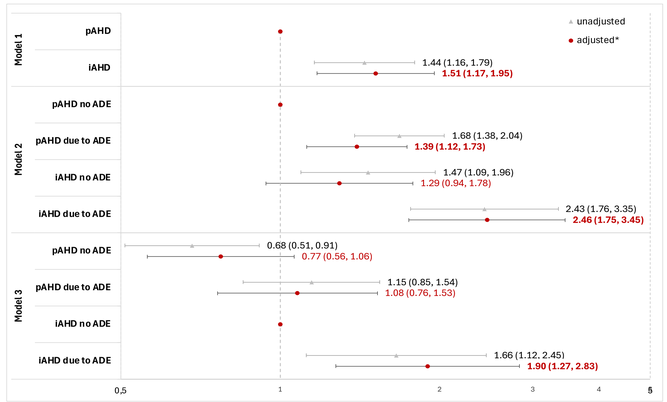


Figure 3: Hazard ratios of all-cause mortality from fitting Cox regression models



* **Confounders for adjusted models:** age, comorbidities (one at a time), CD4 count, smoking/alcohol, employment, sex at birth HIV transmission risk factor, calendar year of AHD diagnosis, education, nationality, third drug. **Significant p-values are shown in bold.**

CONCLUSIONS

- **The incidence of AHD among PWH already in care in Italy has significantly declined over time**, accounting for less than 15% of total AHD cases in the past decade.
- **pAHD and iAHD showed distinct demographic characteristics** with **iAHD more often exhibiting signs of social deprivation** (i.e. injecting drug use, smoking, alcohol abuse and lower education).
- Compared to pAHD, **iAHD was associated with poorer clinical outcomes, particularly in those with a history of ADE**.
- **Further research is needed to elucidate the mechanisms behind this mortality gap** to prevent AHD after charging in care and identify this condition before progression to AIDS.

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